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Essentiality of selenium in the human body: relationship with different diseases

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Abstract

In the present review different aspects related to the essential element selenium in the human organism are considered. A large number of human studies have been performed in order to improve knowledge on the influence of this element in the origin and development of several degenerative diseases. Selenium deficiencies among human beings as well as animals are being recognized worldwide to be related to a number of pathologies. This element has also the special characteristic that the range between its essential and toxic character is very close, and consequently daily dietary intake should be appropriately monitored in individuals. Nevertheless, nowadays there is still a lot of controversy about the optimum dietary level of this element in order to cure or to prevent the appearance of diseases such as cirrhosis, cancer, diabetes, or cardiovascular pathologies. Results obtained in several animal and epidemiological studies have indicated that Se could constitute a dietary factor with protective action against several degenerative diseases.

Keywords: Selenium; Essentiality; Supplementation; Bioavailability; Cancer; Diabetes; Cirrhosis; Cardiopathies

1. Introduction and essentiality of selenium

During recent years, interest concerning selenium has increased considerably due to the combined behavior it can have in humans, as either a toxic or an essential element depending on its levels in the environment and food. Thus, when daily dietary intakes of Se exceed the capacity of the human body to eliminate it, some type of intoxication can appear, and therefore chronic symptoms associated to it such as severe irritations on the respiratory system, a typical metallic taste in the mouth, pulmonary edema, and the characteristic smell of garlic in the breath and sweat due to dimethyl selenide (Bedwall et al., 1993; Diaz et al., 1997).

Despite this it is infrequent that a Se deficiency appears as important such as to compromise an individuals' health, especially in Western countries. Circumstances that predispose patients to low Se concentrations are important from the

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diagnostic point of view (Litov and Combs, 1991). In the human organism selenium has a large number of biological functions.

Selenium is a trace element whose essentiality in mammals was discovered in 1957 (Schwarz and Foltz, 1957). Previously, the only practical biological interest indicated for this element was that high levels of Se caused chronic poisoning called alkali disease in livestock resulting from the consumption of plants cultivated on soils with high Se contents (Levander and Burk, 1994). This toxicological effect appeared in zones where the concentration of plants with a high capacity to accumulate Se was very high. This resulted in intoxication of livestock which were fed such plants and finally to those who consumed the meat products of this livestock or directly fed from intake of these plants. Nevertheless, no direct signs for the essential needs of Se in human nutrition were found until 1979, when a research group from China discovered relationships between the low concentration of Se in the geographical area of Keshan in China and a pathology called Keshan disease which was an endemic congestive cardiomyopathy with myocardial insufficiency (Keshan Disease Research Group, 1979). This disease affected almost exclusively the towns of the mountainous zones of these areas, in which the soya cultivated had a very low Se content, and consequently all food produced there had minimum concentrations of this element. It has been observed that the inhabitants of this region have the lowest serum Se concentrations for non-hospitalized individuals (Yang, 1987).

Keshan disease principally affects children aged between 2 and 10 years, and premenopausal women. Additionally, other important pathologies associated with Se deficiency in humans are muscle problems, digestive alterations, cardiovascular disease and rheumatic disturbances (Neve et al., 1987; Ortuño et al., 1996). Several animal studies have demonstrated that appropriate supplementation with this trace mineral prevented several chronic pathologies, namely hepatic necrosis, pancreatic fibrosis or the degeneration of the striate and cardiac muscles. On the other hand, observations of the changes of Se status and the incidence of Keshan disease showed that new latent and naturally-occurring chronic cases were found in the endemic area even after Se levels had been elevated in the residents to the typical levels determined for the non-endemic area (Xu et al., 1997). This research indicated that although Se deficiency might be a primary pathogenic geogen in the occurrence of this disease, it is rather a conditional predisposing factor than a specific or initiative etiologic factor for the occurrence of Keshan disease (Xu et al., 1997). Consequently, Keshan disease may be the result of several interacting causes including a dominant nutritional deficiency of Se, other nutritional factors (vitamin E, polyunsaturated fatty acids), and an infectious agent (virus) (Levander and Beck, 1997). Further studies are needed in the future in this field to determine the existing inter-relationships among different factors and their capacity to develop the disease.

Selenium has a large number of biological functions in the human organism. The most important and known action is its antioxidant effect because it forms selenocysteine, part of the active center of the glutathione peroxidase enzyme (GSH-Px) (Chappuis and Poupon, 1991; Levander and Burk, 1994). This element is also included in other functionally active selenoproteins as the type 1 iodothyronine 5′-deiodinase which interacts with iodine to prevent abnormal hormone metabolism (Foster and Sumar, 1997). On the other hand, in the cell GSH-Px plays an important function, because the reduced form of this enzyme reduces the hydrogen peroxide and lipidic hydroperoxides at the level of the cytosol and mitochondrial matrix (Chappuis and Poupon, 1991; Simonoff and Simonoff, 1991). Other molecules, such as the vitamin E and superoxide dismutase enzyme also collaborate in this protection against cellular oxygenated by-products (Chappuis and Poupon, 1991; Levander and Burk, 1994; Navarro-Alarcon et al., 1998). Because of its role in the GSH-Px, this element probably interacts with any nutrient that also affects the antioxidant/prooxidant balance of the cell (Levander and Burk, 1994). In this sense, Se has an action overlapping that of vitamin E. This mineral also protects against the toxicity of other heavy metals such as mercury, lead and silver

(Frost, 1983; Cuvin-Aralar and Furness, 1991; Ellingsen et al., 1993; Levander and Burk, 1994). Specifically in fish, the Se levels are high enough to provide protection against Hg toxicity, although the exact mechanisms of interaction between them are not well understood (Cuvin-Aralar and Furness, 1991).

Although food is the main source of Se for man, the dietary Se intake principally depends on the region of origin of the foodstuffs (Tato Rocha et al., 1994; Diaz-Alarcon et al., 1996a) and the protein content. Thus, animal products (meat and fish) tend to be richer in Se than plant materials (Ari et al., 1991; Benemariya, 1992; Diaz-Alarcón, 1995; Diaz-Alarcon et al., 1996b). Nevertheless, in order to establish the correct balance of Se in human beings and animals, it is necessary to estimate the efficacy of the supply of this element in the diet. In a similar manner, such as happens for the remaining trace elements, to determine the total content of them in food is not enough, since it is necessary to know the bioavailability of the Se or the amount absorbed, used and transformed into biologically active forms in the organism (Levander and Burk, 1994; Ortuño et al., 1996); in most foods only a part is available (Favier, 1993).

2. Selenium in diet and foods

In 1980 the Food and Nutrition Board of the United States Research Council proposed an appropriate and estimated safe daily dietary intake of Se for a healthy adult of 50–200 μg/day (Food and Nutrition Board, 1980). Several years later, the same organization, after checking that the maximum activity of the glutathione peroxidase enzyme was reached when the intake of a 60 kg man is 40 μg Se/day, established the recommended dietary allowances (RDA) for this element (Food and Nutrition Board, 1989). Taking into account the body weight and applying a safety factor, depending on the particular idiosyncrasy of individuals, the resulting RDAs were 70 and 55 μg/day for a healthy adult man and woman, respectively. A smaller level was recommended for children considering the body weight and an arbitrary factor related with growing (Litov and Combs, 1991). During the physiological periods of pregnancy and lactation some supplements of Se were considered necessary according to the fetal demands and amounts lost in the human milk (Levander, 1991).

The difficulty for measuring the Se uptake from the diet is one of the principal problems in analytical epidemiological studies. One of the ways to estimate it could be by direct determination of the Se content in meals (duplicate portion sampling), although this method is not used in large studies (Corella Piquer et al., 1991). Additionally, this technique is inconvenient when it is performed for a long period of time; it reflects a wide variation in food consumption and consequently in most of cases a definitive conclusion cannot be obtained in relation to the intake of a determined element. Another alternative would consist of using food composition tables (which collect the Se content in different food) in order to calculate the Se supply; this method is based in the individual consumption of food. Nevertheless, this procedure is inadequate for studies in which the food sources are geographically widely distributed, due to the high variability of the Se concentration in diet of individuals, by the geological differences of farmlands (Paya-Perez et al., 1993; Zhao et al., 1993; Wahl et al., 1994; Diaz-Alarcon et al., 1996a).

The analysis of biological specimens (blood, plasma, serum, erythrocytes, urine, hair, fingernails, etc., for determining Se concentration or glutathione peroxidase activity) which reflect the Se consumption have also been considered in order to estimate the Se dietary intake (Brätter et al., 1991; Maksimovic et al., 1992; Ovaskainen et al., 1993; Garland et al., 1993; Navarro et al., 1995, 1996; Bartfay et al., 1998; Chan et al., 1998; Hagmar et al., 1998). Specifically, plasma would be a short-term indicator and erythrocytes longer-term indicators (Simonoff et al., 1992).

In food the highest Se contents is found in fish products; shrimp has a major ability to accumulate this element and constitutes one of the most important food sources of Se in the diet (Hershey et al., 1988; Zhang et al., 1993; Diaz-Alarcon et al., 1994). Generally, the Se concentration of

foodstuffs depends upon protein contents, as directly observed in soybean (Ferreti and Levander, 1976; Weaver et al., 1988). A similar finding was observed for protein food of animal origin (Oster and Prellwitz, 1989; Van Dokkum et al., 1989; Benemariya et al., 1991, 1993a; Diaz-Alarcon et al., 1994, 1996a), especially the organs such as the kidney and liver that present a higher capacity to accumulate this element (Jaffar and Ashraf, 1989).

There are a number of different factors which can influence the Se contents of foods, namely food processing such as cooking which could produce a loss of 40% by volatilization of the Se present in asparagus and mushrooms when they are boiled for several minutes (Higgs et al., 1972). Some loss in Se content when chicken pieces and fish are roasted, has also been indicated (Tanticharoenkiat et al., 1988; Thomson and Robinson, 1990). Similarly, Bratakos et al. (1988) also checked that the Se content in food diminished from 110 μg to 95 μg after cooking of several foods together. However, other researchers did not find any decrease, and indicate that processes of cooking, aeration or drying, significantly increases the Se content in all food (Zhang et al., 1993). Taking into account this controversy several studies considered more research in this area should be performed in order to clarify the specific influence of different cooking processes on Se content of different foods.

The Se content in food principally depends on the concentration and physico-chemical forms existing in the soil (Tato Rocha et al., 1994). There are some zones where the Se levels in soil are very low (< 0.05 ppm), namely several areas of China, Finland and New Zealand. In these regions the diseases derived from a deficiency of Se in the livestock, and finally their implications in the health of human beings, are well known. Nevertheless, in other regions of high Se concentrations in soils, there is a net excess of this element such as has been observed in Canada, Ireland, some regions of the western USA, some zones of China, France, Germany, etc. (> 5 ppm). Other factors such as the pH and redox potential in soil, the existence of some organic and inorganic compounds, the oxidation state of the element [the absorption of Se^{6+} is higher than that of Se^{4+} (Spallholz, 1994)], type of rocks, nature of draining waters, climatic conditions, etc., would also influence the distribution and nutritional status of this element (Simonoff and Simonoff, 1991; Grandjean et al., 1992; Diplock, 1993; Tato Rocha et al., 1994; Luoma et al., 1995; Voutsa and Samara, 1998). In general, in acid soils, Se is mainly present in the form of selenite which is poorly assimilated and is soluble, while for alkaline farmlands, it is previously oxidized to selenate, which is more soluble and assimilated by crops cultivated on them. Finally, selenate can originate organic compounds of Se (Gondi et al., 1992).

In general the state and Se concentration in food of vegetal origin are highly variable and depend mainly on the soil conditions where they were grown (Levander and Burk, 1994), and on the nature of plants cultivated in them in relation to their capacity to accumulate the Se in the soils (Spallholz, 1994).

It has been previously indicated that the protein content of food is related to Se present. This relationship is due in part to the fact that plants can uptake selenates and selenites from soils. This Se can replace sulfur in the amino acids as selenomethionine, selenocysteine and selenocystathionine due to the physico-chemical similarity existing between them (Simonoff and Simonoff, 1991; Favier, 1993). Furthermore, they would be used in the synthesis of Se-amino acids (mainly, selenomethionine and selenocysteine), and consequently in vegetal proteins (Simonoff and Simonoff, 1991). These Se forms included in the proteins that would finally be utilized by animals in the synthesis of their own proteins thus facilitating their accumulation.

Many studies have been performed in different countries and communities throughout the world, as indicated in Table 1, which summarizes the recent literature on Se intake for healthy adults. As compiled, the Se intakes ranges from < 10 μg/day in Se-deficient areas to approximately 5000 μg/day in those where there exists an endemic selenosis (Robberecht et al., 1994). Dietary intake levels in the study undertaken by our research group in south-eastern Spain is 72.6 μg Se/person per day for healthy adults using a food

analysis sampling technique and consumption data. This result is slightly lower than findings obtained by Mejuto Martí et al. (1986) in north-western Spain (Galicia) of 98 and 92 μg Se/day when diet analysis or food consumption records were used, respectively. In general, intake levels in our study are in the same concentration range as published for other countries. In Finland the effect of a previous fertilizing of soils with sodium selenate significantly increased the daily dietary

Table 1
Daily dietary intake of Se in human beings from several countries

Country (region)	Mean ± S.D. (μg)	Range (μg)	Reference
Belgium	52 ± 16	26–83	Robberecht et al., 1982
Netherlands	78	–	De vos et al., 1984
USA (Beltsville)	82 ± 3	–	Levander and Morris, 1984
Spain (Galicia)	95	–	Mejuto Martí et al., 1986
Greece	110	–	Bratakos et al., 1987
USA (Beltsville)	84 ± 4	–	Levander et al., 1987
USA (Beltsville)	71	–	Schubert et al., 1987
Greece	95	–	Bratakos et al., 1988
Nepal	23 ± 16	–	Moser et al., 1988
Turkey	52 ± 34	–	Muncu et al., 1988
France	–	34–81	Simonoff et al., 1988
France	42	–	Simonoff et al., 1988
Finland	39	–	Varo et al., 1988
Finland	92	–	Varo et al., 1988
Japan	127	–	Yoshida and Yasumoto, 1988
Sweden	40 ± 4	–	Abdulla et al., 1989
Germany (Western)	–	38–48	Oster and Prellwitz, 1989
Japan	97 ± 22	45–135	Suzuki et al., 1989
Italy	90	60–90	Stacchini et al., 1989
Netherlands	72	47–109	Van Dokkum et al., 1989
Denmark	56 ± 28	18–263	Bro et al., 1990
Pakistan	–	64–108	Qureshi et al., 1990
Portugal (Pinhel)	37	7–67	Reis et al., 1990
Denmark	57	–	Tarp et al., 1990
Netherlands	55.9 ± 12.5	–	Van't Veer et al., 1990
USA (South Dakota)	174 ± 91	68–444	Swanson et al., 1990
Finland	28 ± 17	–	Knekt et al., 1991
USA (Ohio)	77 ± 13.6	–	Singh et al., 1991
USA (South Dakota)	85 ± 5	–	Snook, 1991
Greece	100 ± 6	68–727	Bratakos and Ioannou, 1991
USA (Ohio)	240 ± 143	–	Longnecker et al., 1991
USA	–	60–160	Longnecker et al., 1991
New Guinea	20	–	Donovan et al., 1992
Lithuania	100	–	Golubkina et al., 1992
Norway	80	–	Meltzer et al., 1992
Burundi	–	16.9–82.4	Benemariya et al., 1993b
Finland	42.5	–	Ovaskainen et al., 1993
France	48 ± 3	–	Pelus et al., 1994
Belgium	–	28.4–61.1	Robberecht et al., 1994
Mexico (northern)	–	60.6–72.9	Valentine et al., 1994
Spain (south-eastern)	72.6	–	Diaz-Alarcón, 1995
Croatia	27.3	–	Klapec et al., 1998
USA (Alaska)	> 70	–	Nobmann et al., 1998

intake of Se from 39 to 92 μg/person per day (Varo et al., 1988). This finding shows that Se supplementation of the farmlands could be one of the possible ways to increase the Se environmental levels in regions deficient in this element, and therefore in food cultivated there, in order to correct Se deficiencies in the diet.

In our study we checked that type of food or diet is probably the most important variable in determining the amount of Se intake. Specifically, we checked that seafood (Diaz-Alarcon et al., 1994), meat products (Diaz-Alarcón, 1995) and cereals (Diaz-Alarcón, 1995) and overall bread are the foods that mainly contribute to the daily dietary intake of Se in healthy individuals from south-eastern Spain (55% of the total amount), due to their high Se concentrations and frequent consumption in the diet. This finding agrees with the statements of other researchers (Donovan et al., 1992; Srikumar et al., 1992) regarding vegetarians and lactovegetarians have a significantly decreased daily dietary intake of Se, which consequently could induce a deficient Se nutritional status.

3. Selenium supplementation

Taking into consideration all previously discussed, we conclude that overall Se supplementation can be beneficial for individuals overall, in regions where there are very low environmental Se levels. This supplementation trial can be performed directly through the enrichment of some chosen foods with this element or indirectly by a previous fertilization of soils with selenium on which plants were grown (Varo et al., 1988). In order to get the US RDA for Se some countries have implemented a supplementation strategy, as is the case in Finland where in 1984 the government decided to add sodium selenate to the farmlands (Varo et al., 1988). In 1985 the first results were observed resulting in an increase in Se levels present in milk, meat, and eggs from 7 to 8, 4 to 5, and 2 to 3 times, respectively (Varo et al., 1988). Additionally, European legislation allows the addition of sodium selenite to fodder (0.1 mg Se/kg) (Simonoff and Simonoff, 1991).

Another possibility could be the direct Se intake in humans by taking Se supplements or multimicronutrient supplements that include Se in their composition. In the latter years our habits have been intensively influenced by the information from several sources and, consequently, by the publicity about the necessity of the usual consumption of multimicronutrient supplements in the normal diet, as a method of fortifying inadequate diets with a lack of some of these micronutrients such as Se. This is especially important for individuals with nutritional problems, in population groups with a higher risk of deficiency such as children, during infancy or the elderly (Thurnham, 1992). Also it is important for healthy people with a high concern for diet and fitness, or in people who regularly practice any type of sport, since there was a belief that physical activity increased vitamin and mineral requirements (Bazzarre et al., 1993), such as those related to oxidative stress (Chan et al., 1998). This could be an important reason why a majority of athletes ingest large doses of micronutrient supplements. Additionally, the relationship of the body Se status with the origin and development of diseases, namely cancer (Luoma, 1998; Navarro-Alarcon et al., 1998; Psathakis et al., 1998), cardiovascular diseases (Hughes and Ong, 1998; Mihailovic et al., 1998; Navarro-Alarcon et al., 1999a), liver diseases (Loguercio et al., 1997; Guarini et al., 1998), diabetes mellitus (Navarro-Alarcon et al., 1999b) and other degenerative pathologies related to aging (Apostolski et al., 1998; Cornett et al., 1998) and therefore, with the health of individuals, has also contributed in a considerable manner to an increase in the normal consumption of supplements. This fact is yielding a clear influence in the nutritional habits of the general population. In this way, in recent studies performed on the American population, approximately 40% of individuals regularly consume micronutrient supplements (Kim et al., 1993). This trend has been established despite many doubts about the unquestionable recommendation of micronutrient supplementation to the entire population (Lachance, 1994). Overall, healthy subjects who usually have a balanced and varied diet normally intake the appropriate nutritional level of

essential micronutrients such as Se (US RDA, Food and Nutrition Board, 1989).

Despite this, it is necessary to take into consideration the significant and negative relationships that in the later years have been observed in the Se status of patients suffering different degenerative diseases, namely cancer, cirrhosis, cardiovascular diseases, diabetes, etc. Specifically, a significant impairment in the body Se status was observed when serum Se levels in patients were compared against those measured in healthy individuals used as a control group (Loguercio et al., 1997; Luoma, 1998; Mihailovic et al., 1998; Navarro-Alarcon et al., 1998, 1999a,b; Psathakis et al., 1998). Therefore, in the sense of an increase in the healthy state of human beings as a preventive measure, the progressive rise in the number of individuals who regularly consume micronutrient supplements and consequently Se supplements is understood.

There are several pharmacological factors of Se preparations used in human supplementation which influence the Se bioavailability as the physico-chemical form. These include interactions with other micronutrients included in the supplement, the formulation under which these supplements are usually taken, effects derived from their simultaneous administration with specified medications or even the convenience of taking supplements in fasting or meal conditions, and finally timing, dose and schedule of supplementation. We consider that these factors are very interesting as most of studies focus on the influence of dietary factors on Se bioavailability from supplements such as the fiber content, the presence of oxalate, phytate, protein, several polysaccharides, amino acids, etc. Consequently, we consider that more research is necessary in this field in order to obtain better knowledge of the amount of Se biologically available for the human organism from Se supplements used today.

Several studies have been undertaken in order to study the influence of the forms of the Se supplement on its bioavailabilty. In general, animal study trials demonstrate that bioavailability of organic forms of Se (Se-methionine and Se-yeast) is higher than that obtained for inorganic forms (selenite and selenate) (Levander, 1983; Smith and Picciano, 1987), as was also observed in human studies (Litov and Combs, 1991; Favier, 1993; Thomson and Robinson, 1993). Although both inorganic and organic forms cross the intestinal barrier, the differences observed, established a higher bioavailability for Se-methionine and yeast enriched in Se, facilitating a slower decrease in serum Se levels and a longer maintenance of these high levels for several months even after ending the supplementation trial. On the other hand, other studies compared the Se bioavailability between inorganic salts (selenite and selenate), checking that the effect of both Se forms and GSH-Px activity were similar (Korpela, 1988). However, since the selenate is more stable and less toxic than selenite, this researcher pointed out that selenate can be regarded as a more appropriate form for Se supplementation (Korpela, 1988).

4. Selenium bioavailability

Selenium is a micronutrient whose concentrations (which are quite close to each other) can cause deficiency or toxicity; therefore it is of importance to know its abundance or deficiency in food (Jaffe, 1992). In this sense, to know the correct balance of Se in humans and also in animals it is necessary to estimate the efficacy of the supply of this mineral by diet. Therefore, it is not sufficient to measure the total content, but it is important to know the bioavailability or amount absorbed and used by the organism; in most food only a fraction is biologically available (Ortuño et al., 1996). Therefore the Se bioavailabilty depends not only on its absorption by the intestine but also on its conversion to a biologically active form (Foster and Sumar, 1995).

The technique of evaluation of bioavailable Se is based upon the premise that after its absorption conversion into biologically active forms is different for the several chemical forms of Se (Levander et al., 1983). The in vivo evaluation is the unique and safer technique to evaluate the Se bioavailability (Ortuño et al., 1996). Nevertheless, these procedures are very expensive and difficult; therefore the in vitro methods constitute a good

alternative for the study of Se bioavailability, taking the precaution to select the appropriate conditions (Johnson, 1989). On the other hand, there are no perfect animal models in order to study and interpret the micronutrient bioavailability in humans. Taking all this into consideration, to determine the Se bioavailability it is necessary to coordinate the use of in vitro and in vivo methods using cell, animal and human models (Greger, 1992; Levander and Burk, 1994).

In in vivo studies, one effective manner to estimate the bioavailability is by the determination of the GSH-Px activity (Favier, 1993) in blood platelets, which have demonstrated as previously indicated for blood samples, that organic forms enhance the activity of this enzyme compared with selenate or selenite, which can be correlated with the fact that different Se forms follow distinct metabolic pathways in the organism (Thomson et al., 1982). In relation to this, Burk (1986) observed the existence of several Se pathways in the human organism depending on its source. The selenomethionine can be stored in a protein pool when the methionine is limited or catabolized with the release of Se which passes to another pool. On the other hand, the selenocysteine is not stored but it is directly catabolized and the resulting Se goes into a pool to be used later. Selenocysteine can also be incorporated into selenoproteins (Levander and Burk, 1994). The inorganic forms (selenite and selenate) go directly into the pool, from which independent of its origin, all the Se is used in the synthesis of selenoproteins as the GSH-Px and the excess is excreted. If the selenomethionine should be necessary for the cells it would suffer a physiological proteolysis and a delayed release (Favier, 1993). However, when the excretion capacity is overcome, some toxic forms of Se appear in the tissues. Consequently, GSH-Px levels are mainly regulated by the levels of selenocysteine or inorganic forms of Se (Burk, 1986; Hassan et al., 1990; Ekholm et al., 1991; Lane et al., 1991).

Other researchers, after an 8-week supplementation trial developed in rats, determined that the recovery of the GSH-Px activity when compared with the control group (100%) was 98% for selenite, 127% for selenate, 127% for raw beef and 139% for cooked minced beef (Shi and Spallholz, 1994). This finding suggests that the Se bioavailability from raw and cooked ground beef is higher than that for inorganic forms of Se (selenite or selenate), and establishes the positive influence of other components of food, in this case beef, in the availability of the Se present.

Selenium bioavailability has a high enough variability, principally due to the different chemical forms and factors previously indicated that exist in foods. When compared with sodium selenite (100%) the range of Se bioavailability varied from 9% for dry fish to 210% in chickens fed with dehydrated flour of forage (Cantor et al., 1982). In most vegetables, the Se present is highly available (85–100%), while in seafood it ranges from 20 to 50% (Neve et al., 1987), being usually less than 25% (Cantor et al., 1975), despite the usually highest Se content in seafood (Diaz-Alarcón, 1995; Diaz-Alarcon et al., 1996c). Meat products have a bioavailability for Se of approximately 15% (Levander et al., 1983). Finally, dairy products have the lowest bioavailability ranging from $< 2\%$ in ewe milk to 7% in cow and goat milk (Shen et al., 1993).

Other nutrients of diet can also influence the fraction of Se biologically available, as it has been demonstrated for other minerals. In this sense, the way in which phytate and fiber content of diet influences Se availability has been scarcely studied. More research in this area is necessary in order to know exactly the mechanisms through which these components influence Se bioavailability. Preliminary studies about the action of the pectin of diet performed by Gibson (1994) indicated a negative effect on Se absorption.

5. The role of the selenium in different diseases

In recent years, the scientific concern of Se has increased as a result of the descriptive and prospective studies performed in several countries (USA, Germany, Norway, China, Spain, etc.) since it seems that low Se levels could be another factor in the origin of some human diseases as cancer, cardiovascular sclerosis, cirrhosis, diabetes, etc.

It was in 1973 when its presence as a selenocysteine residual in the four active centers of the GSH-Px, as one of the principal antioxidant systems in the organism was identified. Consequently, a deficiency in Se would originate in an impairment in the GSH-Px activity, whose main action is to catalyze the reduction of the organic and inorganic hydroperoxides produced during the oxidative stress of the phospholipids of the membrane, and metabolic oxidation of the xenobiotics (Tato Rocha et al., 1994). This enzyme presents a high affinity by its substrate reducing free radicals to the oxygen at the same rate as its consumption (Florez-Tascón et al., 1993). Today, the GSH-Px is very well known: that Se participates in the lipo-oxygenase pathway, in the organic antioxidant systems together with the catalase, superoxide dismutase, vitamin E, vitamin C, carotenoids, etc., whose principal function is to eliminate the free radicals derived from oxygen such as hydrogen peroxide, organic hydroperoxides, superoxides and hydroxyl radicals (Neve et al., 1987; Chappuis and Poupon, 1991; Simonoff and Simonoff, 1991; Levander and Burk, 1994; Apostolski et al., 1998; Chan et al., 1998). Efficient removal of all these free radicals maintains the integrity of membranes, reduces the risk of cancer, and slows the aging process (Chan et al., 1998), and therefore degenerative diseases. Some of the changes and diseases associated with aging may be explained on the basis of the free radical theory, such as an increase in the frequency of tumors, atherosclerosis and hypertension, immune dysfunction or changes in the central nervous system. It seems that the antioxidant mechanism of the Se would result in an increase in the activities of the phospholipidic hydroperoxide-glutathione peroxidase, by means of which a peroxidation protection of membrane fatty acids, an inhibition of the activity of phospholipase A_2 and an interruption of the arachidonic acid cascade could be reached (Kuklinski et al., 1991). In this sense, taking into consideration the antioxidant activity of this element, several studies indicate that high serum antioxidant and Se levels are related to a lower death rate from coronary heart disease. This was found by Luoma (1998) for inhabitants from Finland. Furthermore, this researcher indicated that serum Se levels increased with the rise of consumption of fish in the diet. The indicated antioxidant activity of the Se seems to be exerted synergistically with vitamin E (Schwarz and Foltz, 1957). Many other studies have confirmed this relationship in human beings and animals, recently in mice it was demonstrated that the simultaneous supplementation with Se (as sodium selenite) and vitamin E (alpha-tocopherol acetate) significantly increased the heart Se concentrations and GSH-Px activities when compared with groups of mice supplemented individually with vitamin E or Se or non-supplemented (Bartfay et al., 1998).

In general, tissues with a high vulnerability to the oxidative stress are those with a high metabolic activity such as liver, heart, diaphragm and striate muscle. This fact explains a Se deficiency in situations of hemolysis, hepatic necrosis, impairment of the immune and inflammatory function and toxic alteration of chemical agents (Tato Rocha et al., 1994). Consequently, this element has a high importance to prevent the cellular injury derived from these pathological situations, because an impairment in the GSH-Px activity cannot be compensated with other non-Se-dependant antioxidant systems.

As considered before, the dietary supply of Se could not be enough to satisfy body needs in areas of low environmental Se levels in farmlands and surrounding areas, where some endemic diseases can exist, namely some regions of New Zealand, Finland and overall in China. There are some pathologies directly related with a low dietary intake of Se in diet as the Keshan and Kashin-Beck diseases, which both affect mainly to children and adolescents. In both diseases a severe Se deficiency and an intense impairment of the GSH-Px in the cellular membranes and erythrocytes were observed (Keshan Disease Research Group, 1979; Moreno-Reyes et al., 1998).

Furthermore, patients submitted to long-term total parenteral nutrition (more than 20–30 days) have a major probability to develop a Se deficiency, as these preparations have very low Se levels (Lane et al., 1987; Levander and Burk, 1994). In addition, other biochemical alterations associated with this situation are found in these

individuals as an impairment in the GSH-Px and an increase in the creatin kinase and transaminase activities. Additionally, in these individuals associated symptoms with deficient Se intake such as muscle ache and heart abnormalities were reversed (Johnson et al., 1981). Normally a low Se level is almost invariably present in patients with severe gastrointestinal disorders who need parenteral supplementation due to gut failure (Rannem et al., 1998).

In the case of digestive alterations and malfunction, some associated states of Se deficiency can appear, as has been observed in alcoholics, cirrhotic individuals, etc. (Korpela et al., 1985). Malabsorption or a rise in the intestinal losses could also produce marginal states of Se deficiency, as it has been indicated in Down's syndrome, cystic fibrosis, celiac disease, or acquired immune deficiency syndrome (AIDS) (Lane et al., 1987; Olmsted et al., 1989; Singh et al., 1991; Varkonyi et al., 1998). The hematologic alterations have also been correlated with a deficit in Se as hemolytic anemia where there is an impairment in the GSH-Px activity of the erythrocyte or Glazman's tromboasteny at which the decrease of the activity in the considered enzyme is established in plaquettes (Neve et al., 1987; Tato Rocha et al., 1994). On the other hand, Se deficiency is common in patients with severe gastrointestinal disorders due mainly to a malabsorption and a lost of Se (Rannem et al., 1998). Nevertheless, for diabetes mellitus controversial results have been obtained. Further studies in this area are needed in order to clarify the implication of Se in the genesis and development of this disease (Navarro-Alarcon et al., 1999b). However, Se induces a sustained improvement of glucose homeostasis in diabetic individuals by an insulin-like action (Berg et al., 1995; Becker et al., 1996; Kimura, 1996), by what supplementation trials could not be discarded.

There is another group of diseases with a high sensibility to the deficit in Se which include not only the pathology derived from its deficiency, but also alterations where this element is not responsible of the pathologic alteration but of the beneficial therapeutic effect. In this group are included, muscular alterations at which an increase in the lipidic peroxidation is produced as the congestive cardiomyopathy and myotonic dystrophy, or those at which a rise in the losses of Se is produced as the Duchenne's disease (Tato Rocha et al., 1994). Additionally, several experimental studies indicated that blood Se levels and GSH-Px activity decreased significantly in patients with cardiovascular diseases (Yegin et al., 1997; Navarro-Alarcon et al., 1999a); therefore some researchers have indicated that these parameters might be used as determinants in an assessment of the severity of the disease (Yegin et al., 1997).

Finally, there is another group of neurologic diseases associated with the increase of the oxidative injury such as multiple sclerosis and Alzheimer's disease (Larner, 1996; Cornett et al., 1998). The deficiency of Se, which may act physiologically as an antagonist of tellurium, in the Alzheimer's brain would also be in keeping with the hypothesis of tellurium toxicity as a factor in the pathogenesis of Alzheimer's disease. It has been reported that Te can damage mitochondria; defects in mitochondrial energy metabolism may be relevant to the pathogenesis of neurodegenerative diseases (Larner, 1996).

It is still controversial whether a low Se level and a reduced activity of the Se-dependent enzyme GSH-Px in blood are associated with an increase risk and poor prognosis of cancer in humans. However, when considering the different tumor stages, a decline of the mean Se level in the most advanced carcinoma group was found. Consequently, a hypothesis of an association between low Se level and advanced tumor disease is established (Jendryczko et al., 1997; Psathakis et al., 1998). Nevertheless, from literature data it cannot be decided whether this phenomenon is more likely to be a consequence or a causative factor for development and course of the disease. However, it is evident that damages to normal tissue, especially to DNA enzymes and membranes caused by free radicals is one mechanism in tumorigenesis, tumor progression and therapeutic consequence (Hehr et al., 1997); therefore a radioprotective effect of Se is verified by in vitro and in vivo data. Despite this, improving life

quality and secondary cancer prevention with supplementation of Se has to be proven in future prospective randomized studies.

Deficiency symptoms of Se developed in patients receiving long-term parenteral nutrition are dilated cardiomyopathy which resembles Keshan disease (Itokawa, 1996). Consequently, this researcher indicates a requirement of Se for human adults from total parenteral nutrition as 0.02–0.05 mg/day in order to prevent associated Se deficiencies.

5.1. Selenium and cancer

Evidence of selenium-dependent enzymes having specific carcinostatic action by destroying reactive oxygen has been reviewed. Protection of humans and animals from cancer by selenium has been indicated by epidemiological relationship (Simonoff et al., 1992; Spallholz, 1994; Hehr et al., 1997) and by experimental studies of Se and known carcinogens in the development of specific cell lines. In this sense, a radioprotective effect of sodium selenite has been verified in rectal cancer patients with no side effects (Hehr et al., 1997). In mice studies Se supplementation with sodium selenite produced an inhibition in almost all of the skin lesions induced by the dimethylbenzoanthracene (DMBA) carcinogenic agent (Horvath and Ip, 1983). In the rat liver the aflatoxin B_1 acts as a potent hepatotoxic and hepatocarcinogen agent due to its capacity to induce lipidic peroxidation. This activity was reduced considerably by a Se pretreatment with Se and vitamin E as antioxidants (Shen et al., 1994). Similarly, the protective effect when Se acts synergically with vitamin E has been indicated for colon and breast cancers provoked by the dimethylhydrazine and DMBA, respectively (Birt, 1986).

Several mechanisms for which selenium has been proposed for its inhibiting effect on cancer, namely the modulation of cellular division rate, the metabolic alteration of some carcinogenic agents with a decrease in the formation of carcinogenic metabolites, or cellular protection by an antioxidant system against severe oxidation and even by the stimulation of the immune system (Navarro-Alarcon et al., 1998). In any case, Se plays an important role in a variety of biochemical reactions as a cofactor of the glutathione peroxidase enzyme (Chappuis and Poupon, 1991; Levander and Burk, 1994), which also prevents the initiation and progress of neoplastic events by protecting cells against hydroperoxide ions causing free radical formation.

In several epidemiologic studies an inverse relationship between body Se status measured as blood, serum or plasma concentrations or GSH-Px activity of erythrocytes or plaquettes, has been observed. In Table 2 the serum and plasma Se levels obtained in patients with different types of cancer is compared with those corresponding to healthy controls. In most human studies, included in Table 2, the existence of a statistical significant difference was obtained. Specifically, in cancer patients the plasma or serum Se levels were significantly lower in patients than in healthy controls ($P < 0.05$). These low peripheral Se levels cannot therefore be considered carcinogenic promoters, but the result of a decrease in the efficiency of the organism's mechanisms against oxidative stress and its consequences in the genesis and development of the cancer. This finding would establish that the low Se status of cancer patients is more a consequence than a cause of the illness, mainly for the gastrointestinal cancer, for which low plasma Se may be related to insufficient intake, urinary loss, redistribution or even insufficient levels of carrier proteins (Simonoff et al., 1992).

In several epidemiological studies included in Table 2 we observe that the significant decrease of serum or plasma Se levels affected different types of cancer, such as pancreatic, colon, gastric, lung, breast, uterine, respiratory, digestive, hematological or gynecological cancer. Others found that serum or plasma Se levels and the general element status were similar in patients (colon, lung, nasopharyngeal and diverse cancer) and controls (Table 2) (Kuklinski et al., 1991; Kabuto et al., 1994; Lajtman et al., 1994; Backovic et al., 1998). Moreover, other researchers did not find any protective effect of higher serum Se levels in benign or malignant colonic tumors (Nelson et al., 1995). However, some researchers have indicated the recommendation of Se use in nutritio-

Table 2
Serum and plasma Se levels in patients with different diseases (cancer, cardiovascular disease and diabetes mellitus) and healthy controls

Disease	Patients (μg/l)	Healthy controls (μg/l)	Significance	Reference
Cancer (location)				
Pancreatic	102.0 ± 3.1	112 ± 2	Yes[a]	Burney et al., 1989
Gastric	63 ± 15	85 ± 8	Yes[a]	Liu, 1991
Diverse	52	78	Yes[a]	Simonoff and Simonoff, 1991
Colon	78.6	62.4	No	Kuklinski et al., 1991
Diverse	47.0 ± 3.7	57.1 ± 2.6	Yes[a]	Simonoff et al., 1992
Gastric	56.2	78.5	Yes[a]	Pawlowicz et al., 1993
Colon	63.0 ± 18	89.0 ± 13.0	Yes[a]	Caroli et al., 1994
Diverse	75.3	117.0	Yes[a]	Gupta et al., 1994
Lung	–	–	No	Kabuto et al., 1994
Lung	–	–	Yes[a]	Hu, 1993
Nasopharyngeal	–	–	No	Lajtman et al., 1994
Breast	–	–	Yes[a]	Sharma et al., 1994
Breast	–	–	Yes[a]	Van der Brandt et al., 1994
Diverse	–	–	Yes[a]	Wasowicz et al., 1994
Uterine	–	–	Yes[a]	Lou et al., 1995
Pancreatic	–	–	Yes[a]	Segal et al., 1995
Diverse	–	–	No	Backovic et al., 1998
Respiratory	42.6 ± 2.42	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1998
Digestive	51.8 ± 26.6	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1998
Hematological	59.5 ± 20.9	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1998
Gynecological	55.3 ± 27.5	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1998
Cardiovascular				
Myocardial infarction	52.0	55.0	Yes[a]	Salonen et al., 1982
Diverse	59.0	80.0	Yes[a]	Simonoff et al., 1986
Myocardial infarction	52.9	77.4	Yes[a]	Koehler et al., 1988
Atherosclerosis	29.6	77.4	Yes[a]	Koehler et al., 1988
Congestive heart failure	29.6	104.6	Yes[a]	Le Bouil et al., 1992
Diverse	52.0 ± 3.3	57.1 ± 2.6	Yes[a]	Simonoff et al., 1992
Myocardial infarction	114.4 ± 15.1	113.2 ± 15.7	No	Salvini et al., 1995
Cardiomyopathy	48.0 ± 25.0	77.0 ± 16.0	Yes[a]	Cenac et al., 1996
Arteriosclerosis	–	–	No	Ondrus et al., 1996
Arterial hypertension	–	–	Yes[a]	Yegin et al., 1997
Chronic heart disease	–	–	Yes[a]	Mihailovic et al., 1998
Coronary atherosclerosis	–	–	Yes[a]	Mihailovic et al., 1998
Myocardial infarction	58.7 ± 27.2	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1999a
Ischemic cardiomyopathy	55.5 ± 16.7	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1999a

Table 2 (*Continued*)

Disease	Patients (μg/l)	Healthy controls (μg/l)	Significance	Reference
Diabetes mellitus (DM)				
Diabetic children	–	–	Yes[b]	Gebre-Medhin et al., 1984
Diabetes	78.0	95.0	Yes[a]	Schlienger et al., 1988
Diabetes	–	–	Yes[a]	Simonoff and Simonoff, 1991
Diabetic children, Hungary	89.0	68.0	Yes[b]	Cser et al., 1993
Diabetic children, Germany	101.0	68.0	Yes[b]	Cser et al., 1993
Diabetic pregnant women	–	–	Yes[a]	Tawardowska-Saucha et al., 1994
Diabetes	–	–	No	Holecek et al., 1995
Diabetes	–	–	No	Wang et al., 1995
Non-insulin dependent diabetes	–	–	No	Armstrong et al., 1996
Diabetic individuals	64.9 ± 22.8	74.9 ± 27.3	Yes[a]	Navarro-Alarcon et al., 1999a

[a]A statistical significant decrease was observed ($P < 0.05$).
[b]A statistical significant increase was observed ($P < 0.05$).

nal prophylaxis and chemical prevention against cancer at a dose of 50–100 μg Se/day, or even as a co-adjuvant in chemotherapy during the cancer treatment in whose case the dose sequentially could increase up to 200 μg Se/day (Simonoff and Simonoff, 1991). Taking into account all these contradictory results, and despite most of studies are directed to the beneficial effect of Se in the prevention of cancer disease, general preventive measures based on indiscriminate Se supplementation are not yet justifiable.

Despite that, in some human studies no significant differences between serum or plasma Se levels of cancer patients and those found for healthy controls were observed, nonetheless a tendency to a decrease in serum Se level with increasing extension and the progress of the disease was found (Caroli et al., 1994; Lajtman et al., 1994). This result was obtained in 22 patients with ulcerative colitis and 22 sex-, age- height- and weight-matched controls from Poland (Jendryczko et al., 1997). These researchers indicated that this inverse correlation between the serum Se concentration and the extension of the disease could be caused by a decreased absorption of Se from the diseased colon in ulcerative colitis. A similar finding was indicated for patients with colorectal cancer (Psathakis et al., 1998), for whom an association between low Se level and advanced tumor disease was determined. Gupta et al. (1994) demonstrated in cancer patients that the Se level decreased not only with the progress of disease but also with the recurrence of it.

Several mechanisms through which Se would exert its protective effect against cancer have been proposed, namely modulation of cell division, metabolic alteration of some carcinogens, cell protection against oxidative damage as an antioxidant, stimulation of the immune system, inhibition of the activity of hepatic enzymes or activation of detoxicant enzymes.

Usually, patients with different types of cancer present a serum mean Se level of 58 μg/l against the 78 μg/l determined in healthy subjects. Additionally, the Se distribution into serum Se and erythrocyte Se differs depending on whether individuals have cancer or not. Although it is still not known which is the mechanism responsible for this blood Se decrease in cancer patients, it could be related to the loss of antioxidant activity of the

organism against the oxidative stress induced by the increase in free radicals which would induce the appearance of carcinogenic or toxic substances. However, the possibility that the low blood Se concentrations in carcinogenic processes could result in a sequestration of Se by the tumor cells or even by a low food supply as the cause of the tumor cannot be discarded (Simonoff and Simonoff, 1991; Zachara et al., 1997). Zachara et al. (1997) studied the Se concentration and glutathione peroxidase activity in cancerous and tumor-free lung tissue of 84 lung cancer patients. These authors indicated that the tumor Se level was higher by 66.6% ($P < 0.0001$) and GSH-Px activity by 49.5% ($P < 0.0001$) than in adjacent tumor-free tissue, despite of the cause of these increased levels is not understood and requires future studies.

5.2. Selenium and cardiovascular disease

For some time now, selenium has been related to the prevention of cardiovascular diseases. An inverse correlation between the incidence of the coronary disease in human beings and animals, and environmental or blood Se levels has been found (Corella Piquer et al., 1991; Simonoff and Simonoff, 1991; Levander and Burk, 1994; Navarro-Alarcon et al., 1999a). Therefore, a serum Se level of < 55 μg/l has been previously associated with an enhanced risk of coronary heart disease (Macpherson et al., 1995).

A review of the literature showed that most of the studies found a significant decrease of serum or plasma Se concentrations in patients with different cardiopathies (acute myocardial infarction, atherosclerosis, congestive heart failure, cardiomyopathy, arterial hypertension, chronic heart disease, ischemic cardiomyopathy, coronary atherosclerosis, etc.) (Table 2). However, it is not clear if such differences are etiological factors or biological consequences of diverse cardiopathies. On the other hand, some theories indicate that very low Se levels measured in patients with cardiopathies are indicators of deficiency in Se, which could contribute to enhance the risks (Corella Piquer et al., 1991). Other epidemiological studies did not show this statistically-significant decrease in serum or plasma Se levels in patients with cardiovascular diseases (Salvini et al., 1995; Yegin et al., 1997) (Table 2).

In individuals with cardiopathies with significant impairment in serum Se levels, the urine Se concentrations were also significantly lower than those found in the control group (Blotcky et al., 1988; Navarro-Alarcon et al., 1999a). This result correlates with the fact that the significant decrease of serum Se levels observed in patients later causes a significant impairment of urine Se elimination. This reaction of the organism would contribute to regulate the Se homeostasis, due to its protective effect against that pathology, in order to maintain the body Se status as high as possible. Nevertheless, additional studies are necessary in order to confirm this finding and to specifically know how the organism adjusts Se elimination by several available pathways in order to keep the Se homeostasis not only in patients with cardiopathies but also in other diseases.

The precise mechanism by which low plasma Se levels act in these diseases is not yet known. Some authors have indicated that low Se concentrations in atherosclerosis may facilitate the formation of lipid hydroperoxides, which could attack vascular endothelium (Turk et al., 1980). Others have established that selenium modified prostaglandin synthesis, improving thromboxanes in platelets and diminishing prostacyclin concentration in vascular endothelium (Mehta, 1983; Neve, 1996). In this sense, Se as an antioxidant agent is related to prostaglandin metabolism, since it acts as a GSH-Px cofactor (Turk et al., 1980; Miyake, 1994; Neve, 1996). Another mechanism would be due to the protective action of Se against the toxicity of heavy metals (Neve, 1996). Growing evidence suggests that oxidative modification of low-density lipoprotein (LDL) may be of particular importance in the pathogenesis of cardiopathies because oxidized LDL exhibits proatherogenic effects (Odeh and Cornish, 1995).

The relationship between Se and vitamin E deficit in cardiovascular diseases could be theoretically explained by the action of macrophages. These would be responsible for the initial atheroma plates on injuries due to lipid oxidation. Macrophages together with ceroid then cause an

enhancement of oxidized lipids, as determined in early atheroma plates. This activity of the microbiocide oxidative systems of the macrophages could constitute an essential phase in the development of the atheroma plate (Mitchinson, 1984). An antioxidant deficit would increase the consequences of the disease. Platelet aggregation occurs after lipid hydroperoxide attack on endothelium cells of blood vessels, which could cause a narrowing of the intima (Thompson, 1991). Although several epidemiological studies have indicated a significant association between high levels of serum Se levels and a decreased risk for occurrence and mortality from cardiovascular diseases (Salonen et al., 1982; Luoma et al., 1995; Yegin et al., 1997; Luoma, 1998), other data have provided no evidence for this association (Simonoff and Simonoff, 1991; Strain, 1994; Salvini et al., 1995).

The antioxidant mechanism of Se as a preventive mineral in the development and genesis of cardiovascular diseases through its protective role against LDL oxidation should be considered in future long-term longitudinal studies concomitantly with remaining nutrients involved in the oxidative stress as antioxidants, namely vitamin E, vitamin C, carotenoids, zinc, copper, etc., and other antioxidant food components as flavonoids. The oxidative stress is a very complex process occurring continuously in the human organism at which many substrates [prooxidant (homocysteine and iron) and antioxidant agents] are involved. Therefore, future intervention trials of supplementation should be focused in the concomitant administration and study of all these agents in order to have a better knowledge of their resulting effect in the oxidation process, and consequently in cardiovascular diseases. In this sense, Nyyssonen et al. (1994) established that Se and other antioxidants (ascorbic acid, alpha-tocopherol and beta-carotene) have a protective effect against oxidation, shown as a higher resistance against the oxidation of serum LDL- and VLDL-cholesterol, in a double-blind clinical trial. Consequently, it is necessary to determine which is the most appropriate and healthy diet supplemented with antioxidants and phytonutrients for prevention and promotion of optimum cardiovascular health.

The importance of Se as an active component of the GSH-Px in oxidative stress has also been indicated in several studies performed on healthy adults as a control group (Jossa et al., 1991; Coudray et al., 1997), institutionalized elderly subjects (Gámez et al., 1997) and patients with AMI (Navarro-Alarcon et al., 1999a). These individuals showed positive significant relationships among serum Se levels with: general lipemia (Coudray et al., 1997), plasma total-cholesterol as well as LDL-cholesterol (Gámez et al., 1997), and total-cholesterol (Jossa et al., 1991; Navarro-Alarcon et al., 1999a). Triglycerides as vehicles of fatty acids in the blood [saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA)] and cholesterol are the target substances for the oxidation. Consequently, despite that in AMI patients a significant reduction in serum Se levels occurred when compared with healthy controls (Table 2), this impairment is lower when higher lipemia levels were found. This finding supports the important role of Se as antioxidant agent in these patients even though cardiovascular disease has already occurred (Navarro-Alarcon et al., 1999a). Nevertheless, the mechanism of the increase of serum Se concentrations with lipemia is unknown. Therefore, future research is needed in the coming years to confirm this relationship in other types of cardiopathies as well as to exactly know the mechanism through which this enhancement is established.

Epidemiological studies have produced some intriguing results, but have not indicated unequivocally that a high intake of Se leads to a decreased cardiovascular disease risk. We conclude that the antioxidant atherosclerosis hypothesis is promising, but the results of long-term intervention trials are still to be awaited. Consequently, preventive action based on Se supplementation as an organism's antioxidant is therefore not justifiable as yet.

5.3. Selenium and diabetes mellitus

Diabetes mellitus has been related to alteration in the homeostasis of certain elements such as selenium (Simonoff and Simonoff, 1991). This pathology is a major health problem throughout

the world where approximately 2–3% of individuals are affected. Proper care of diabetics is essential and good management reduces the frequency of complications (Anderson and Bazel Geil, 1994). This chronic disease requires long-term goals including freedom from diabetic complications. Among them, atherosclerosis is the most common complication of diabetes (Figuerola, 1992; Anderson and Bazel Geil, 1994). Diabetic men and women have a 2–5-fold higher risk of coronary heart disease, stroke and peripheral vascular disease than matched non-diabetic individuals (Navarro-Alarcon et al., 1999b). Therefore, reducing risk of vascular disease requires improved glycemic control, normal blood pressure, and appropriate serum lipoprotein and triglyceride levels (Anderson and Bazel Geil, 1994).

Additionally, the erythrocyte and serum Se concentrations, as well as several enzyme activities [GSH-Px, superoxide dismutase (SOD), peroxidase, catalase] are frequently reduced (Simonoff and Simonoff, 1991). The epidemiological studies performed in erythrocytes of diabetic patients have indicated an enhanced lipidic peroxidation and GSH-Px activity as compared with healthy controls. Nevertheless, the SOD activity was impaired as much as that the enhancement of the GSH-Px activity was not able to compensate it. The final result was an increase in peroxidation (Shah et al., 1983). As far as we can understand, free radicals are new in the origin of damage undergone by diabetics, and specifically in injuries of tissues specially sensitive to the oxidation, such as cardiovascular, ocular, renal and neurological tissues (Figuerola, 1992).

In diabetic patients another typical change is the high susceptibility to infectious agents. This is in part due to the fact that the polymorphonuclear leukocytes act as though properties (susceptibility against infectious agents) were impaired (Foster, 1989). Therefore, patients with diabetes mellitus often suffer from infections. Besides, in the tissular inflammation response these leukocytes induce the intervention of the leukotriene synthesis by the lipooxygenase pathway (Simonoff and Simonoff, 1991).

A review of the literature shows that there is controversy among the different clinical studies performed on the serum Se levels in diabetic patients (Table 2). Some researchers found a significant decrease in patients with different types of diabetes mellitus (Schlienger et al., 1988; Simonoff and Simonoff, 1991; Tawardowska-Saucha et al., 1994; Navarro-Alarcon et al., 1999b). Others observed that serum selenium levels and the corporal element status were similar in patients and controls (Holecek et al., 1995; Wang et al., 1995; Armstrong et al., 1996). Nevertheless, other investigators even found a statistically-significant increase in Se concentrations in diabetic patients to those determined in the control group (Gebre-Medhin et al., 1984; Cser et al., 1993), which was interpreted as a possible protective mechanism of the vascular system against the aggressiveness of prooxidant agents and free radicals (Gebre-Medhin et al., 1984). Taking into consideration these contradictory results and the sparse literature in this field, future research is needed in order to have a better knowledge of the Se metabolism in diabetic subjects, which could help us to decide the convenience of Se supplementation in these patients.

An increased lipid peroxidation and reduced antioxidant status may contribute to the development of complications in diabetes. The Se supplementation as selenate (Becker et al., 1996) or selenomethionine + tocopherol acetate (Douillet et al., 1996) decreased plasma glucose levels in diabetic rats. This finding has also been observed in diabetic human beings (Wang et al., 1995). The Se induces a sustained improvement of glucose homeostasis in diabetic individuals by an insulin-like action (Berg et al., 1995; Becker et al., 1996; Kimura, 1996). Taking into consideration all this, a Se supplementation with this element cannot be discarded because this element facilitates a better homeostatic regulation of the blood glucose levels and a significant increase in the activity of the GSH-Px enzyme.

5.4. Selenium and hepatopathies

Se is an essential element whose deficit in rats might produce a necrosis of hepatocytes similar to those derived from an excessive consumption of alcohol, overall when it is associated with low

vitamin E concentrations (Simonoff and Simonoff, 1991). Then, structural changes produced originally in the endoplasmic reticule of hepatocytes would cause microsomal peroxidations.

Alcohol as a toxic substance for the human organism enhances free radical production and the toxic consequences derived from their appearance in the body. Alcohol metabolism increase the lipidic oxidation of cell membranes, mainly of the hepatocytes, provoking a chronic transient state characterized by a leukocytes infiltration and an enhancement in the collagen formation (Välmäki et al., 1983). Additionally, in alcoholism a decrease in the serum Se is established which is more pronounced when the gravity of the hepatopathy progresses (Dworkin et al., 1985; Conri et al., 1988).

In alcoholic subjects significantly lower plasma concentrations of vitamin E, ascorbic acid and Se have been determined when compared with levels measured in controls with a low alcohol intake, while malonaldehyde levels which is the main marker of the oxidative stress is augmented in alcoholic individuals (Aaseth et al., 1986). Other authors confirmed that after a period of abstinence (21 days) from alcoholic drinks vitamin E and Se serum plasma concentrations did not change while those of malonaldehyde and ascorbic acid decreased significantly (Lecomte et al., 1994).

Selenium deficit of the alcoholic individual might be due to a low nutritional supply of this element. This Se deficit seems to be more a consequence of the alcoholism since an excessive dietary intake of alcohol would produce a decrease of the remaining food consumption, and therefore a limitation of the amount of Se ingested from diet (Robberecht and Deelstra, 1994). This nutritional deficit of Se would produce an impairment in the GSH-Px activity, and consequently a decrease in the catalytic destruction of hydroperoxides which are augmented by the high alcohol intake. As a consequence of this process an accumulation of these toxic products in the liver would occur, which is also submitted to the own toxicity of the alcohol. In these conditions a nutritional deficit of Se as well as of other antioxidants would enhance the toxic action of this drug (Thuluvath and Triger, 1992).

In the literature review included in Table 3, we

Table 3
Serum and plasma Se levels in patients with different hepatic pathologies and healthy controls

Disease	Patients (μg/l)	Healthy controls (μg/l)	Significance	Reference
Hepatopathy	–	–	Yes[a]	Thuluvath and Triger, 1992
Hepatopathy	38.0	95.0	Yes[a]	Dworkin et al., 1985
Hepatopathy	–	–	Yes[a]	Korpela et al., 1985
Hepatopathy	–	–	Yes[a]	Aaseth et al., 1986
Hepatopathy	35.0	72.8	Yes[a]	Conri et al., 1988
Cirrhosis	–	–	Yes[a]	Capocaccia et al., 1991
Alcoholic damage of liver	–	–	No	Nemaia et al., 1991
Hepatoma	–	–	Yes[a]	Casaril et al., 1994
Severe liver diseases	–	–	Yes[a]	Lecomte et al., 1994
Chronic liver diseases	–	–	Yes[a]	Loguercio et al., 1997
Cirrhosis	41.0 ± 12.4	74.9 ± 27.3	Yes[a]	Perez-Valero, 1997
Hepatitis	49.7 ± 15.6	74.9 ± 27.3	Yes[a]	Perez-Valero, 1997
Alcoholic cirrhosis	–	–	Yes[a]	Guarini et al., 1998

[a]A statistical significant decrease was observed ($P < 0.05$).

observe that most of studies measured significantly lower serum and plasma Se concentrations in patients with different grades of hepatocellular injury than those determined for healthy controls. The only study of those included in this table (Table 3) for which a non-significant decrease in serum Se levels in patients with liver disease was that performed by Nemaia et al. (1991). When the liver injury was caused by toxic substances by alcohol a significant decrease in the serum or plasma Se levels was also observed in these patients (Dworkin et al., 1985; Korpela et al., 1985; Aaseth et al., 1986; Conri et al., 1988; Thuluvath and Triger, 1992).

In the confirmed case of the alcoholism incidence on the serum Se levels it would be interesting to take into account the results obtained by Dworkin et al. (1985) and Conri et al. (1988). These authors divided individuals included in the study in non-alcoholic healthy subjects as control group, alcoholic individuals with normal values for hepatic enzymes (alanine amine transferase and aspartate amine transferase) (Conri et al., 1988), alcoholic individuals with five times higher values than normal for indicated hepatic enzymes, and alcoholic individuals with severe hepatic disease. These researchers pointed out that the progressive enhancement in the hepatic injury produced a major decrease in the serum Se levels (Dworkin et al., 1985; Conri et al., 1988), as was also found in patients with different diseases in south-eastern Spain (Perez-Valero, 1997).

Similar findings were observed in animal studies when an intense necrosis and lipidic peroxidation were provoked by the administration of hepatotoxic substances (Burk et al., 1995). This effect was prevented when a Se dose was administered to these animals.

Despite the fact that some authors did not find any protective effect of Se when the liver is submitted to endotoxins (Shibayama et al., 1994), the Se supplementation in the hepatic disease should not be discarded, although it would be necessary to study in the future which is the most appropriate dose of Se and the moment to initiate the supplementation trial.

6. Conclusions

From results found in the different studies included in the present review for different pathologies (cancer, cardiovascular disease, diabetes mellitus, hepatopathies, etc.), the use of serum selenium levels as diagnostic markers of them cannot be accepted. While there is a statistical difference between mean serum values between the two groups (patients and controls), there is little difference between the mean values and more importantly, there is a marked overlap between the two ranges (mean $\pm$ S.D.). When clinically considering whether a test is useful or not, the predictive value of a test (percentage of a time does a positive test accurately indicate the patient has disease, or a negative test indicate the patient does not have the disease) should be considered, together the *t*-test results (Navarro-Alarcon et al., 1998). Given the marked overlap between the two ranges of the populations (the means are within approx. $1/2$ S.D.) the predictive values are low; there is a statistical significance between the means, but selenium cannot be used to determine whether or not a patient has a specific disease.

Nevertheless, the recommendation of a Se supplementation for patients undergoing different pathologies in whose beginning the oxidative stress is involved, cannot be discarded, mainly due to the Se function as a cofactor of the GSH-Px enzyme. Additionally, future research is needed in order to exactly know the potential preventive use and dose of this element in healthy individuals.

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